

SUPPLEMENTARY MATERIAL

Supplementary Methods

Detailed search strategy

Embase.com

((('folinic acid'/exp AND fluorouracil/exp AND irinotecan/exp AND oxaliplatin/exp AND 'drug combination'/exp AND ('pancreas cancer'/de OR 'pancreas tumor'/de OR 'pancreas adenoma'/de OR 'pancreas adenocarcinoma'/de OR 'pancreas carcinoma'/de OR 'pancreas islet cell carcinoma'/de OR (pancrea* NEAR/3 (cancer* OR neoplas* OR tumo* OR adenocarcinom* OR carcinom* OR adenom*)):ab,ti)) OR (Folfirinox):ab,ti)

Medline (Ovid)

((Leucovorin/ AND fluorouracil/ AND irinotecan.mp. AND oxaliplatin.mp. AND Drug Combinations/ AND (exp Pancreatic Neoplasms/ OR (pancrea* ADJ3 (cancer* OR neoplas* OR tumo* OR adenocarcinom* OR carcinom* OR adenom*)),ab,ti.)) OR (Folfirinox).ab,ti.)

Cochrane

(Folfirinox):ab,ti

Web-of-science

TS=(Folfirinox)

Scopus

TITLE-ABS-KEY(Folfirinox)

Google scholar

Folfirinox

References Excluded studies after full text assessment, *n*=30

Only other regimen than FOLFIRINOX, *n*=10

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No (B)RPC included, n=15

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Language other than English, n=2

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Non-original studie, n=1

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Patients included in other studies, n=2

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Supplementary Table 1. Methodological quality assessment according to Critical Appraisal Skill Program (CASP).

Study [reference]	Clear aim	Recruitment	Accurately measured exposure	Accurately measured outcome	Confounding factors identified	Confounding factors accounted	Follow-up complete enough	Follow-up long enough	Precise statistical results presented	Do you believe results	Ability to generalize results	In accordance with existing evidence	Implications of study in practice
Paniccia et al. 2014[1]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No
Christians et al. 2014[2]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	Yes	No
Katz et al. 2016[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Okada et al. 2016[4]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Shaib et al. 2016[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yoo et al. 2017[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Itchins et al. 2017[7]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Shrestha et al. 2017[8]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Boone et al. 2013[9]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No
Ferrone et al. 2015[10]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	No	No	No
Addeo et al. 2015[11]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes
Khushman et al. 2015[12]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	No
Pietrasz et al. 2015[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes
Mellon et al. 2015[14]	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Blazer et al. 2015[15]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No
Badiyan et al. 2016[16]	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Kim et al. 2016[17]	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No	No	No
Vogel et al. 2017[18]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	No
Grose et al. 2017[19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Tinchon et al. 2013[20]	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	No
Peddi et al. 2012[21]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No
Mahaseth et al. 2013[22]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	No
Moorcraft et al. 2014[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Stein et al. 2016[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

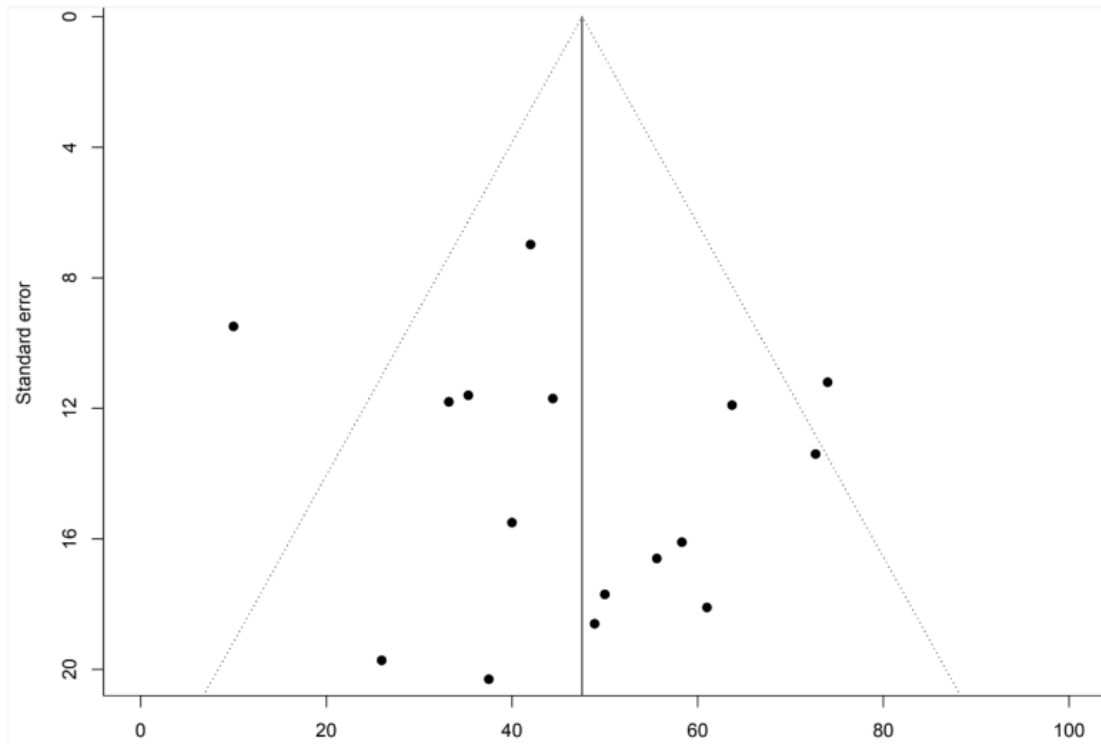
Supplementary Table 2. Survival outcomes reported for BRPC patients treated with neoadjuvant FOLFIRINOX.

Study [reference]*	No. of patients	Median follow-up*, months (IQR)	Median OS, months (95% CI)	Median PFS, months (95% CI)
Paniccia et al. 2014 [1]	18	14.5 (10-17)	25.0	14.0
Katz et al. 2016 [3]	22	NR	21.7 (16-nr)	NR
Shaib et al. 2016 [5]	13	18.0	11.0 (6-nr)	5.7 (3-33)
Yoo et al. 2017 [6]	18	24.1 (14-32)	21.2 (14-28)	16.8 (9-24)
Itchins et al. 2017 [7]	14	34.8	25.9 (12-nr)	NR
Pietrasz et al. 2015 [13]	47	38.2 (29-47)†	nr	16.5†
Kim et al. 2016 [17]	19	41.4†	34.2†	21.3†

* Studies not shown in this table did not report survival outcomes for BRPC patients specifically, or did not report survival at all. NR = Not Reported. nr = not reached. IQR = interquartile range. CI = confidence interval. OS = overall survival. PFS = progression-free survival.

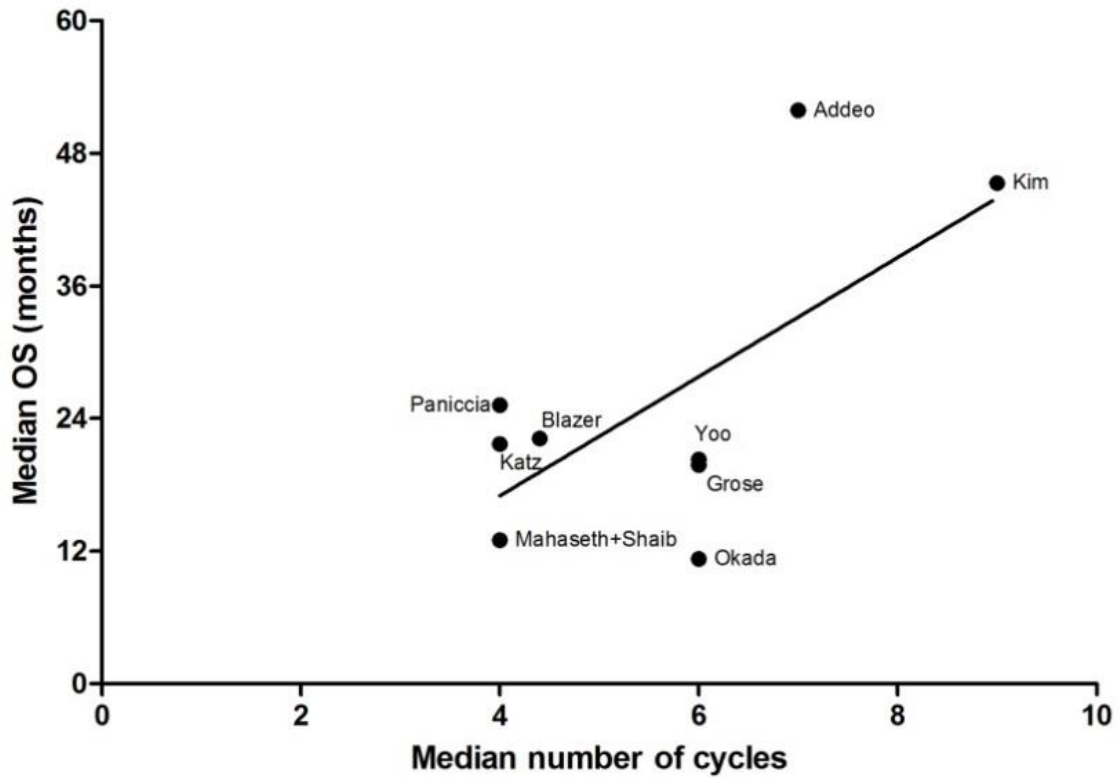
† Resected patients only.

Supplementary Figures

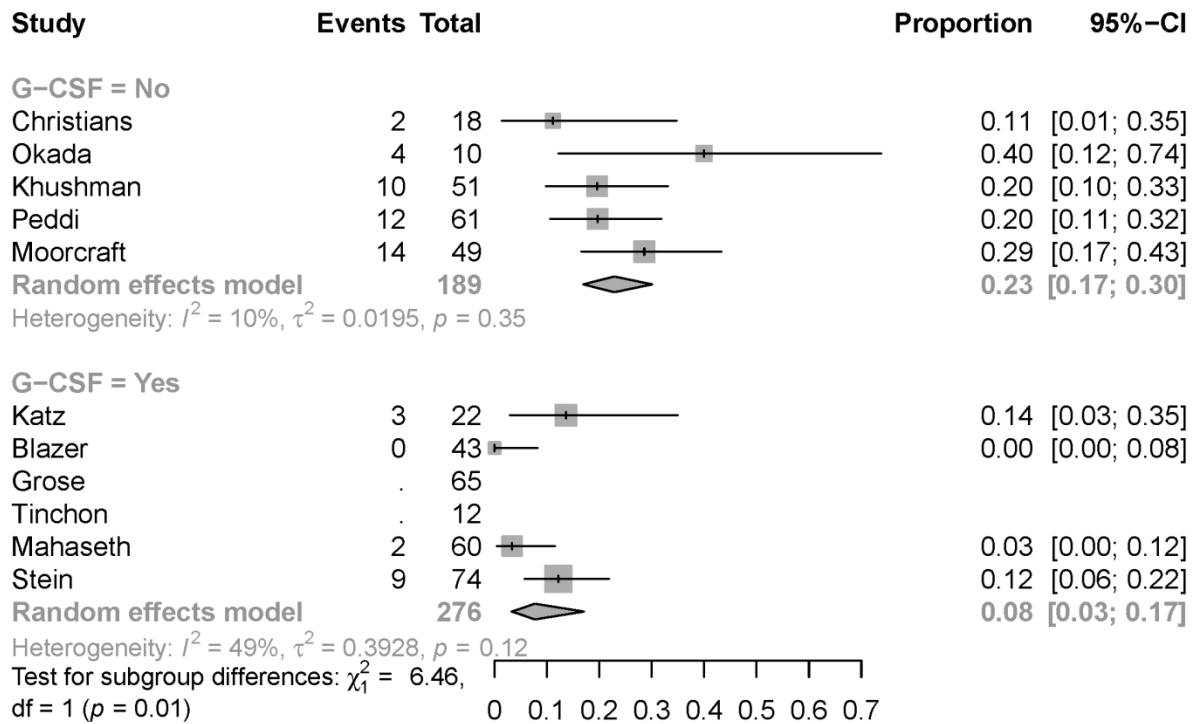


Supplementary Figure 1: Funnel plot of the 2-year OS of studies.

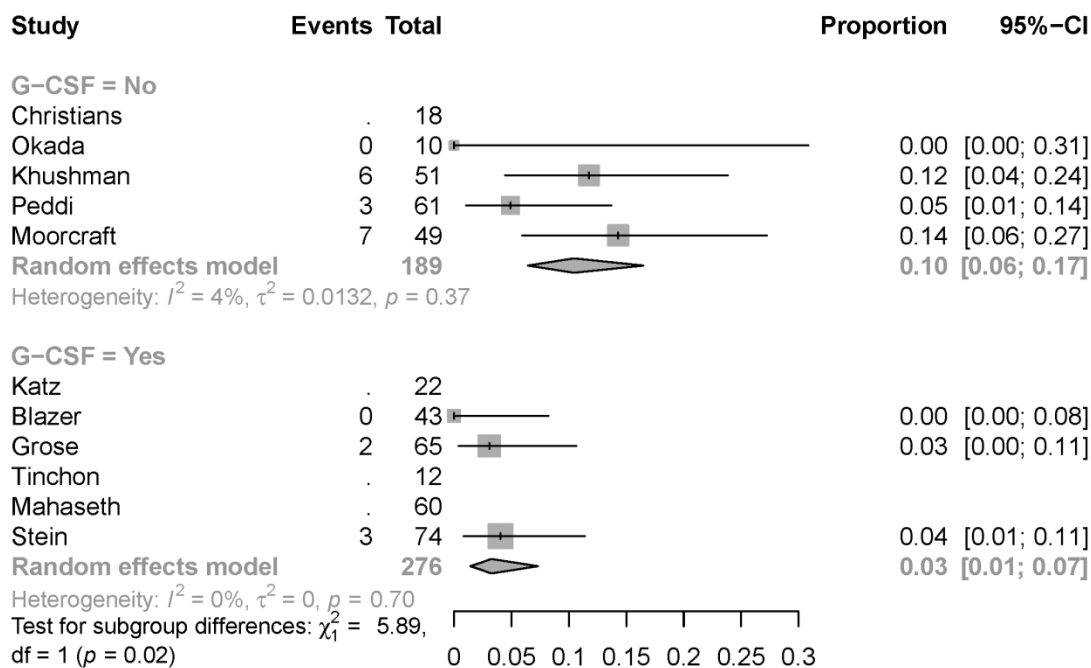
Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only BRPC patients. Three studies are not shown in this funnel plot as Peddi et al.[21] and Mellon et al.[14] included no patients surviving at least 2 years, and Addeo et al.[11] did not have a sufficient number of events to calculate the standard error. OS = overall survival. BRPC = borderline resectable pancreatic cancer



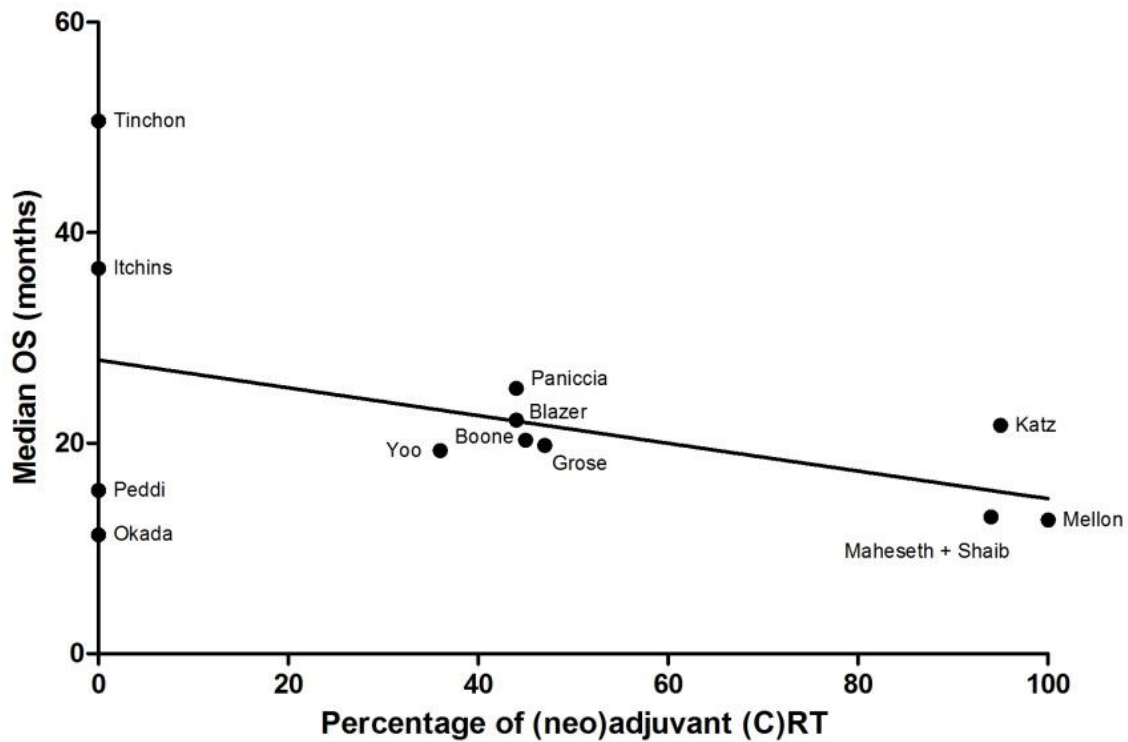
Supplementary Figure 2: Median number of administered neoadjuvant FOLFIRINOX cycles and median OS of studies. Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only BRPC patients. ($p = 0.05$). Linear regression analysis was performed. P-value was calculated using a two-sided F test. OS = overall survival. BRPC = borderline resectable pancreatic cancer.



Supplementary Figure 3: Forest plots showing reported grade 3 or 4 adverse event rates in studies with and without G-CSF prophylaxis: neutropenia ($p = 0.01$). p -value was calculated using a two-sided Q-test and a random effects model. G-CSF = granulocyte-colony stimulating factor. CI = confidence interval.



Supplementary Figure 4: Forest plots showing reported of grade 3 or 4 adverse event rates in studies with and without G-CSF prophylaxis: febrile neutropenia. ($p = 0.02$) p -value was calculated using a two-sided Q-test and a random effects model. G-CSF = granulocyte-colony stimulating factor. CI = confidence interval.



Supplementary Figure 5: (Neo)adjuvant (C)RT after neoadjuvant FOLFIRINOX and median OS of studies. Kaplan-Meier analysis of patient-level OS was used for estimation of median study OS, including only BRPC patients. Two studies are not shown in this figure as Addeo et al.[11] and Kim et al.[17] only included patients who underwent a resection. ($p = 0.14$). Linear regression analysis was performed. P-value was calculated using a two-sided F test. OS = overall survival. BRPC = borderline resectable pancreatic cancer.

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